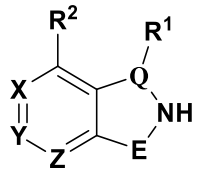
the therapeutic window, enabling sufficient target inhibition in the tumor while avoiding dose-limiting toxicity in cancer patients.

SUMMARY

[0005a] In an aspect of the present disclosure, there is provided a compound of formula I-1:



I-1

or a pharmaceutically acceptable salt thereof, wherein:

E is -C(O)-, -C(R^E)$_2$-, -C(R^E)$_2$C(R^E)$_2$-, -C(S)-, -S(O)$_2$-, -OC(O)-, -N(R^E)C(O)-, -C(O)N(R^E)-, or -C(R^E)$_2$C(O)-;

Q is CH, C(R^Q), or N;

X is CH, C(R^X), or N;

Y is CH, C(R^Y), or N;

Z is CH, C(R^Z), or N;

R^1 is -L^1-R^{1A};

R^2 is -L^2-R^{2A};

each instance of R^E is independently H or -L^E-R^{EA};

R^Q is -L^Q-R^{QA};

R^X is -L^X-R^{XA};

R^Y is -L^Y-R^{YA};

R^Z is -L^Z-R^{ZA}; or

two instances of R^E are taken together with their intervening atoms to form a 3-8 membered saturated or partially unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-12 membered saturated or partially unsaturated bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein each ring is substituted with n instances of R^{EEC};

R^Q and R^1 are taken together with their intervening atoms to form a 4-8 membered saturated or partially unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-12 membered saturated or partially unsaturated bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein each ring is substituted with p instances of R^{Q1C};

R^Y and R^Z are taken together with their intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said ring is substituted with q instances of R^{YZC};

each of L^1, L^2, L^E, L^Q, L^X, L^Y, and L^Z is independently a covalent bond, or a C_{1-4} bivalent saturated or unsaturated, straight or branched hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by $-CH(R^L)-$, $-C(R^L)_2-$, C_{3-6} cycloalkylene, C_{3-6} heterocycloalkylene, -N(R)-, -N(R)C(O)-, -N(R)C(NR)-, -N(R)C(NOR)-, -N(R)C(NCN)-, -C(O)N(R)-, $-N(R)S(O)_2-$, $-S(O)_2N(R)-$, -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -S(O)- , or $-S(O)_2-$;

R^{1A} is R^A or R^B substituted by r^1 instances of R^{1C};

R^{2A} is R^A or R^B substituted by r^2 instances of R^{2C};

R^{EA} is R^A or R^B substituted by r^3 instances of R^{EC};

R^{QA} is R^A or R^B substituted by r^4 instances of R^{QC};

R^{XA} is R^A or R^B substituted by r^5 instances of R^{XC};

R^{YA} is R^A or R^B substituted by r^6 instances of R^{YC};

R^{ZA} is R^A or R^B substituted by r^7 instances of R^{ZC};

R^L is R^A or R^B substituted by r^8 instances of R^{LC};

each instance of R^A is independently oxo, deuterium, halogen, -CN, $-NO_2$, -OR, $-SF_5$, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)_2F$, -S(O)R, $-S(O)NR_2$, -S(O)(NR)R, -S(O)(NCN)R, -S(NCN)R, -C(O)R, -C(O)OR, $-C(O)NR_2$, -C(O)N(R)OR, -OC(O)R, $-OC(O)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, $-N(R)C(O)NR_2$, $-N(R)C(NR)NR_2$, $-N(R)S(O)_2NR_2$, $-N(R)S(O)_2R$, $-P(O)R_2$, -P(O)(R)OR, or $-B(OR)_2$;

each instance of R^B is independently a C_{1-6} aliphatic chain; phenyl; naphthyl; cubanyl; adamantyl; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic

heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 5-12 membered saturated or partially unsaturated bicyclic carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

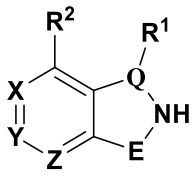
each instance of R^{1C}, R^{2C}, R^{EC}, R^{QC}, R^{XC}, R^{YC}, R^{ZC}, R^{LC}, R^{EEC}, R^{Q1C}, and R^{YZC} is independently oxo, deuterium, halogen, -CN, $-NO_2$, -OR, $-SF_5$, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)_2F$, -S(O)R, $-S(O)NR_2$, -S(O)(NR)R, -C(O)R, -C(O)OR, $-C(O)NR_2$, -C(O)N(R)OR, -OC(O)R, $-OC(O)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, $-N(R)C(O)NR_2$, $-N(R)C(NR)NR_2$, $-N(R)S(O)_2NR_2$, $-N(R)S(O)_2R$, $-P(O)R_2$, -P(O)(R)OR, $-B(OR)_2$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each instance of R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

two R groups on the same nitrogen are taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur; and

each of n, p, q, r^1, r^2, r^3, r^4, r^5, r^6, r^7, and r^8 is independently 0, 1, 2, 3, 4, or 5.

[0005b] In another aspect of the present disclosure, there is provided a compound of formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

E is -C(O)-, -C(R^E)$_2$-, -C(R^E)$_2$C(R^E)$_2$-, -C(S)-, -S(O)$_2$-, -OC(O)-, -N(R^E)C(O)-, -C(O)N(R^E)-, or -C(R^E)$_2$C(O)-;

Q is CH, C(R^Q), or N;

X is CH, C(R^X), or N;

Y is CH, C(R^Y), or N;

Z is CH, C(R^Z), or N;

R^1 is -L^1-R^{1A};

R^2 is -L^2-R^{2A};

each instance of R^E is independently H or -L^E-R^{EA};

R^Q is -L^Q-R^{QA};

R^X is -L^X-R^{XA};

R^Y is -L^Y-R^{YA};

R^Z is -L^Z-R^{ZA}; or

two instances of R^E are taken together with their intervening atoms to form a 3-8 membered saturated or partially unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-12 membered saturated or partially unsaturated bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein each ring is substituted with n instances of R^{EEC};

R^Q and R^1 are taken together with their intervening atoms to form a 4-8 membered saturated or partially unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-12 membered saturated or partially unsaturated bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein each ring is substituted with p instances of R^{Q1C};

R^Y and R^Z are taken together with their intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said ring is substituted with q instances of R^{YZC};

each of L^1, L^2, L^E, L^Q, L^X, L^Y, and L^Z is independently a covalent bond, or a C_{1-4} bivalent saturated or unsaturated, straight or branched hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by $-CH(R^L)-$, $-C(R^L)_2-$, C_{3-6} cycloalkylene, C_{3-6} heterocycloalkylene, -N(R)-, -N(R)C(O)-, -N(R)C(NR)-, -N(R)C(NOR)-, -N(R)C(NCN)-, -C(O)N(R)-, $-N(R)S(O)_2-$, $-S(O)_2N(R)-$, -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -S(O)- , or $-S(O)_2-$;

R^{1A} is R^A or R^B substituted by r^1 instances of R^{1C};

R^{2A} is R^A or R^B substituted by r^2 instances of R^{2C};

R^{EA} is R^A or R^B substituted by r^3 instances of R^{EC};

R^{QA} is R^A or R^B substituted by r^4 instances of R^{QC};

R^{XA} is R^A or R^B substituted by r^5 instances of R^{XC};

R^{YA} is R^A or R^B substituted by r^6 instances of R^{YC};

R^{ZA} is R^A or R^B substituted by r^7 instances of R^{ZC};

R^L is R^A or R^B substituted by r^8 instances of R^{LC};

each instance of R^A is independently oxo, deuterium, halogen, -CN, $-NO_2$, -OR, $-SF_5$, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)_2F$, -S(O)R, $-S(O)NR_2$, -S(O)(NR)R, -C(O)R, -C(O)OR, $-C(O)NR_2$, -C(O)N(R)OR, -OC(O)R, $-OC(O)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, $-N(R)C(O)NR_2$, $-N(R)C(NR)NR_2$, $-N(R)S(O)_2NR_2$, $-N(R)S(O)_2R$, $-P(O)R_2$, -P(O)(R)OR, or $-B(OR)_2$;

each instance of R^B is independently a C_{1-6} aliphatic chain; phenyl; naphthyl; cubanyl; adamantyl; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 5-12 membered saturated or partially unsaturated bicyclic carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each instance of R^{1C}, R^{2C}, R^{EC}, R^{QC}, R^{XC}, R^{YC}, R^{ZC}, R^{LC}, R^{EEC}, R^{Q1C}, and R^{YZC} is independently oxo, deuterium, halogen, -CN, $-NO_2$, -OR, $-SF_5$, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)_2F$, -S(O)R, $-S(O)NR_2$, -S(O)(NR)R, -C(O)R, -C(O)OR, $-C(O)NR_2$, -C(O)N(R)OR, -OC(O)R, $-OC(O)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, $-N(R)C(O)NR_2$, $-N(R)C(NR)NR_2$, $-N(R)S(O)_2NR_2$, $-N(R)S(O)_2R$, $-P(O)R_2$, -P(O)(R)OR, $-B(OR)_2$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each instance of R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

two R groups on the same nitrogen are taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur; and

each of n, p, q, r^1, r^2, r^3, r^4, r^5, r^6, r^7, and r^8 is independently 0, 1, 2, 3, or 4.

[0005c] In a further aspect of the present disclosure, there is provided a compound selected from those set forth in Table 1, or a pharmaceutically acceptable salt thereof.

[0005d] In another aspect of the present disclosure, there is provided a pharmaceutical composition, comprising a compound disclosed herein, and a pharmaceutically acceptable carrier.

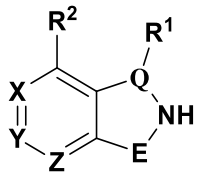
[0005e] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or the pharmaceutical composition disclosed herein, in the manufacture of a medicament for inhibiting PI3Kα signaling activity in a subject.

[0005f] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or the pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating a PI3Kα-mediated disorder in a subject.

[0005g] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or the pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating a cellular proliferative disease in a subject.

[0005h] In another aspect of the present disclosure, there is provided a compound disclosed herein, or the pharmaceutical composition disclosed herein, for use in therapy.

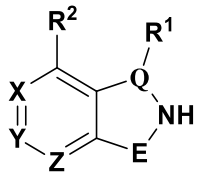
[0006] In some examples, the present disclosure provides a compound of formula I-1:



I-1

or a pharmaceutically acceptable salt thereof, wherein each of R^1, R^2, Q, E, X, Y, and Z is as defined in examples and classes and subclasses herein.

[0007] In some examples, the present disclosure provides a compound of formula I:



I

or a pharmaceutically acceptable salt thereof, wherein each of R^1, R^2, Q, E, X, Y, and Z is as defined in examples and classes and subclasses herein.

[0008] In some examples, the present disclosure provides a pharmaceutical composition comprising a compound of formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant, or diluent.

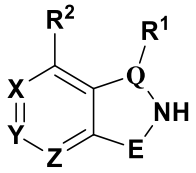
[0009] In some examples, the present disclosure provides a method of treating a PI3Kα-mediated disorder comprising administering to a patient in need thereof a compound of formula I, or composition comprising said compound.

[0010] In some examples, the present disclosure provides a process for providing a compound of formula I, or synthetic intermediates thereof.

[0011] In some examples, the present disclosure provides a process for providing pharmaceutical compositions comprising compounds of formula I.

What is claimed is:

1. A compound of formula I-1:



I-1

or a pharmaceutically acceptable salt thereof, wherein:

E is -C(O)-, -C(R^E)$_2$-, -C(R^E)$_2$C(R^E)$_2$-, -C(S)-, -S(O)$_2$-, -OC(O)-, -N(R^E)C(O)-, -C(O)N(R^E)-, or -C(R^E)$_2$C(O)-;

Q is CH, C(R^Q), or N;

X is CH, C(R^X), or N;

Y is CH, C(R^Y), or N;

Z is CH, C(R^Z), or N;

R^1 is -L^1-R^{1A};

R^2 is -L^2-R^{2A};

each instance of R^E is independently H or -L^E-R^{EA};

R^Q is -L^Q-R^{QA};

R^X is -L^X-R^{XA};

R^Y is -L^Y-R^{YA};

R^Z is -L^Z-R^{ZA}; or

two instances of R^E are taken together with their intervening atoms to form a 3-8 membered saturated or partially unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-12 membered saturated or partially unsaturated bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein each ring is substituted with n instances of R^{EEC};

R^Q and R^1 are taken together with their intervening atoms to form a 4-8 membered saturated or partially unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-12 membered saturated or partially

unsaturated bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein each ring is substituted with p instances of R^{Q1C};

R^Y and R^Z are taken together with their intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said ring is substituted with q instances of R^{YZC};

each of L^1, L^2, L^E, L^Q, L^X, L^Y, and L^Z is independently a covalent bond, or a C_{1-4} bivalent saturated or unsaturated, straight or branched hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by $-CH(R^L)-$, $-C(R^L)_2-$, C_{3-6} cycloalkylene, C_{3-6} heterocycloalkylene, -N(R)-, -N(R)C(O)-, -N(R)C(NR)-, -N(R)C(NOR)-, -N(R)C(NCN)-, -C(O)N(R)-, $-N(R)S(O)_2-$, $-S(O)_2N(R)-$, -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -S(O)- , or $-S(O)_2-$;

R^{1A} is R^A or R^B substituted by r^1 instances of R^{1C};

R^{2A} is R^A or R^B substituted by r^2 instances of R^{2C};

R^{EA} is R^A or R^B substituted by r^3 instances of R^{EC};

R^{QA} is R^A or R^B substituted by r^4 instances of R^{QC};

R^{XA} is R^A or R^B substituted by r^5 instances of R^{XC};

R^{YA} is R^A or R^B substituted by r^6 instances of R^{YC};

R^{ZA} is R^A or R^B substituted by r^7 instances of R^{ZC};

R^L is R^A or R^B substituted by r^8 instances of R^{LC};

each instance of R^A is independently oxo, deuterium, halogen, -CN, $-NO_2$, -OR, $-SF_5$, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)_2F$, -S(O)R, $-S(O)NR_2$, -S(O)(NR)R, -S(O)(NCN)R, -S(NCN)R, -C(O)R, -C(O)OR, $-C(O)NR_2$, -C(O)N(R)OR, -OC(O)R, $-OC(O)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, $-N(R)C(O)NR_2$, $-N(R)C(NR)NR_2$, $-N(R)S(O)_2NR_2$, $-N(R)S(O)_2R$, $-P(O)R_2$, -P(O)(R)OR, or $-B(OR)_2$;

each instance of R^B is independently a C_{1-6} aliphatic chain; phenyl; naphthyl; cubanyl; adamantyl; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 5-12 membered saturated or partially unsaturated bicyclic carbocyclic ring; a 3-7 membered

saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

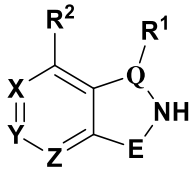
each instance of R^{1C}, R^{2C}, R^{EC}, R^{QC}, R^{XC}, R^{YC}, R^{ZC}, R^{LC}, R^{EEC}, R^{Q1C}, and R^{YZC} is independently oxo, deuterium, halogen, -CN, -NO_2, -OR, -SF_5, -SR, -NR_2, -$S(O)_2R$, -$S(O)_2NR_2$, -$S(O)_2F$, -S(O)R, -$S(O)NR_2$, -S(O)(NR)R, -C(O)R, -C(O)OR, -$C(O)NR_2$, -C(O)N(R)OR, -OC(O)R, -$OC(O)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, -$N(R)C(O)NR_2$, -$N(R)C(NR)NR_2$, -$N(R)S(O)_2NR_2$, -$N(R)S(O)_2R$, -$P(O)R_2$, -P(O)(R)OR, -$B(OR)_2$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each instance of R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

two R groups on the same nitrogen are taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur; and

each of n, p, q, r^1, r^2, r^3, r^4, r^5, r^6, r^7, and r^8 is independently 0, 1, 2, 3, 4, or 5.

2. A compound of formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

E is -C(O)-, -C(R^E)$_2$-, -C(R^E)$_2$C(R^E)$_2$-, -C(S)-, -S(O)$_2$-, -OC(O)-, -N(R^E)C(O)-, -C(O)N(R^E)-, or -C(R^E)$_2$C(O)-;

Q is CH, C(R^Q), or N;

X is CH, C(R^X), or N;

Y is CH, C(R^Y), or N;

Z is CH, C(R^Z), or N;

R^1 is -L^1-R^{1A};

R^2 is -L^2-R^{2A};

each instance of R^E is independently H or -L^E-R^{EA};

R^Q is -L^Q-R^{QA};

R^X is -L^X-R^{XA};

R^Y is -L^Y-R^{YA};

R^Z is -L^Z-R^{ZA}; or

two instances of R^E are taken together with their intervening atoms to form a 3-8 membered saturated or partially unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-12 membered saturated or partially unsaturated bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein each ring is substituted with n instances of R^{EEC};

R^Q and R^1 are taken together with their intervening atoms to form a 4-8 membered saturated or partially unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-12 membered saturated or partially unsaturated bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein each ring is substituted with p instances of R^{Q1C};

R^Y and R^Z are taken together with their intervening atoms to form a 4-7 membered partially unsaturated or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said ring is substituted with q instances of R^{YZC};

each of L^1, L^2, L^E, L^Q, L^X, L^Y, and L^Z is independently a covalent bond, or a C_{1-4} bivalent saturated or unsaturated, straight or branched hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by -CH(R^L)-,

-C(R^L)$_2$-, C_{3-6} cycloalkylene, C_{3-6} heterocycloalkylene, -N(R)-, -N(R)C(O)-, -N(R)C(NR)-, -N(R)C(NOR)-, -N(R)C(NCN)-, -C(O)N(R)-, -N(R)S(O)$_2$-, -S(O)$_2$N(R)-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -S(O)- , or -S(O)$_2$-;

R^{1A} is R^A or R^B substituted by r^1 instances of R^{1C};

R^{2A} is R^A or R^B substituted by r^2 instances of R^{2C};

R^{EA} is R^A or R^B substituted by r^3 instances of R^{EC};

R^{QA} is R^A or R^B substituted by r^4 instances of R^{QC};

R^{XA} is R^A or R^B substituted by r^5 instances of R^{XC};

R^{YA} is R^A or R^B substituted by r^6 instances of R^{YC};

R^{ZA} is R^A or R^B substituted by r^7 instances of R^{ZC};

R^L is R^A or R^B substituted by r^8 instances of R^{LC};

each instance of R^A is independently oxo, deuterium, halogen, -CN, -NO$_2$, -OR, -SF$_5$, -SR, -NR$_2$, -S(O)$_2$R, -S(O)$_2$NR$_2$, -S(O)$_2$F, -S(O)R, -S(O)NR$_2$, -S(O)(NR)R, -C(O)R, -C(O)OR, -C(O)NR$_2$, -C(O)N(R)OR, -OC(O)R, -OC(O)NR$_2$, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)NR$_2$, -N(R)C(NR)NR$_2$, -N(R)S(O)$_2$NR$_2$, -N(R)S(O)$_2$R, -P(O)R$_2$, -P(O)(R)OR, or -B(OR)$_2$;

each instance of R^B is independently a C_{1-6} aliphatic chain; phenyl; naphthyl; cubanyl; adamantyl; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 5-12 membered saturated or partially unsaturated bicyclic carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each instance of R^{1C}, R^{2C}, R^{EC}, R^{QC}, R^{XC}, R^{YC}, R^{ZC}, R^{LC}, R^{EEC}, R^{Q1C}, and R^{YZC} is independently oxo, deuterium, halogen, -CN, -NO$_2$, -OR, -SF$_5$, -SR, -NR$_2$, -S(O)$_2$R, -S(O)$_2$NR$_2$, -S(O)$_2$F, -S(O)R, -S(O)NR$_2$, -S(O)(NR)R, -C(O)R, -C(O)OR, -C(O)NR$_2$, -C(O)N(R)OR, -OC(O)R, -OC(O)NR$_2$, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)NR$_2$,

-N(R)C(NR)NR_2, -N(R)$S(O)_2NR_2$, -N(R)$S(O)_2$R, -P(O)R_2, -P(O)(R)OR, -$B(OR)_2$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each instance of R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

two R groups on the same nitrogen are taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur; and

each of n, p, q, r^1, r^2, r^3, r^4, r^5, r^6, r^7, and r^8 is independently 0, 1, 2, 3, or 4.

3. The compound of claim 1 or 2, wherein the compound is:

(a) a compound of formula III:



III

or a pharmaceutically acceptable salt thereof;

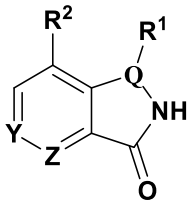
(b) a compound of formula IV:



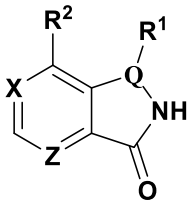
IV

or a pharmaceutically acceptable salt thereof;

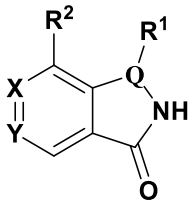
(c) a compound of formula V, VI, or VII:



V



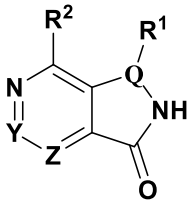
VI



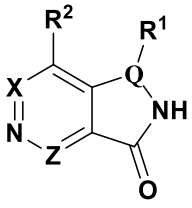
VII

or a pharmaceutically acceptable salt thereof;

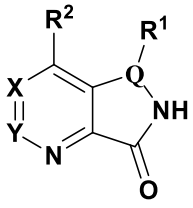
(d) a compound of formula VIII, IX, or X:



VIII



IX



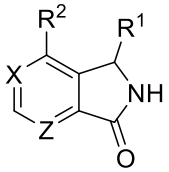
X

or a pharmaceutically acceptable salt thereof;

(e) a compound of formula XI, XII, or XIII:



XI



XII



XIII

or a pharmaceutically acceptable salt thereof; or

(f) a compound of formula XIV, XV, or XVI:



XIV



XV



XVI

or a pharmaceutically acceptable salt thereof.

4. The compound of any one of the preceding claims, wherein X is CH.

5. The compound of claim 1 or 2, wherein the compound is a compound of formula XXVIII:



XXVIII

or a pharmaceutically acceptable salt thereof.

6. The compound of any one of the preceding claims, wherein Z is CH or N.

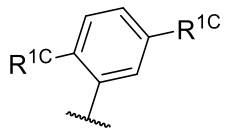
7. The compound of any one of the preceding claims, wherein L^1 is a covalent bond.

8. The compound of any one of the preceding claims, wherein:

(a) R^{1A} is R^B substituted by r^1 instances of R^{1C};

(b) R^{1A} is phenyl or an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein R^{1A} is substituted by r^1 instances of R^{1C};

(c) R^{1A} is phenyl substituted by r^1 instances of R^{1C}; or

(d) R^1 is  .

9. The compound of any one of the preceding claims, wherein each instance of:

(a) R^{1C} is independently halogen, -CN, -O-(C_{1-6} aliphatic), or C_{1-6} aliphatic; wherein each C_{1-6} aliphatic is optionally substituted with one or more halogen atoms; or

(b) R^{1C} is independently halogen or C_{1-3} aliphatic optionally substituted with 1-3 halogen.

10. The compound of any one of the preceding claims, wherein:

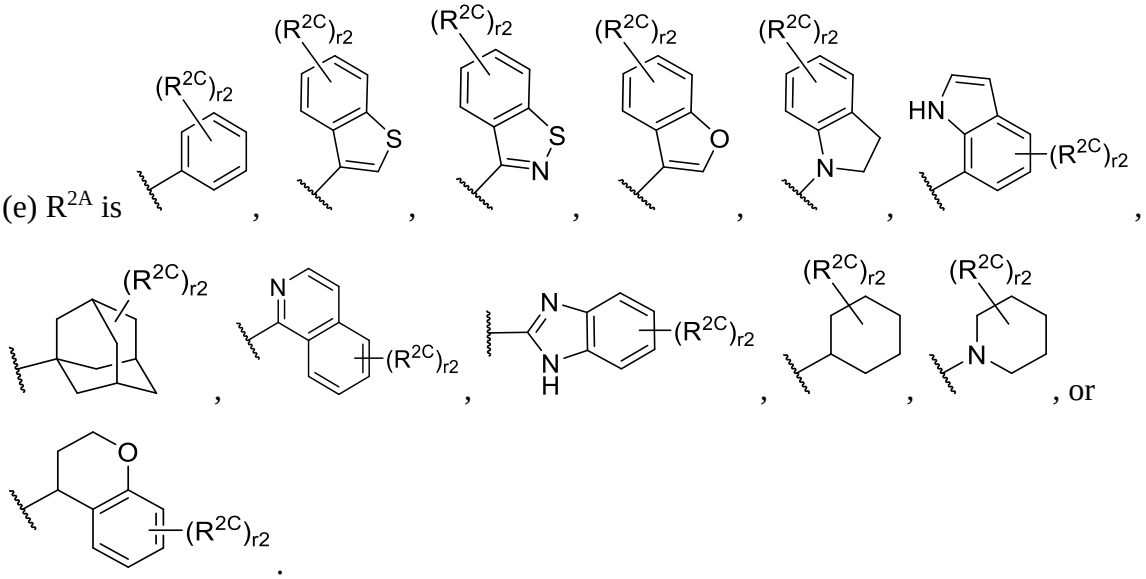
(a) R^2 is -N(H)C(O)-R^{2A}, -N(H)C(O)N(H)-R^{2A}, -C(O)N(H)-R^{2A}, -N(H)-R^{2A}, -$S(O)_2CH_2$-R^{2A}, -$CH_2S(O)_2$-R^{2A}, or -C(H)(CH_3)OH;

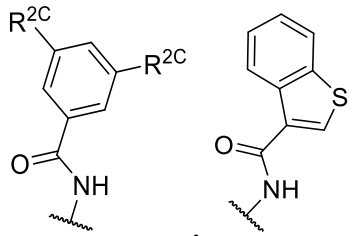
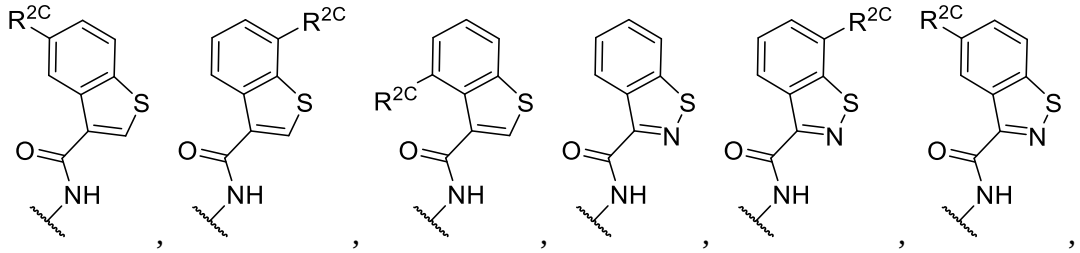
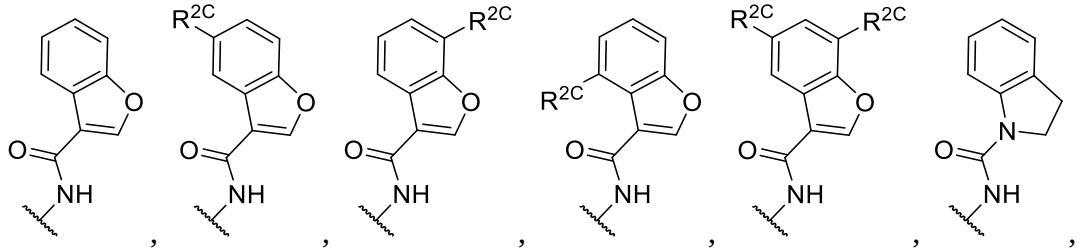
(b) R^2 is -N(H)C(O)-R^{2A};

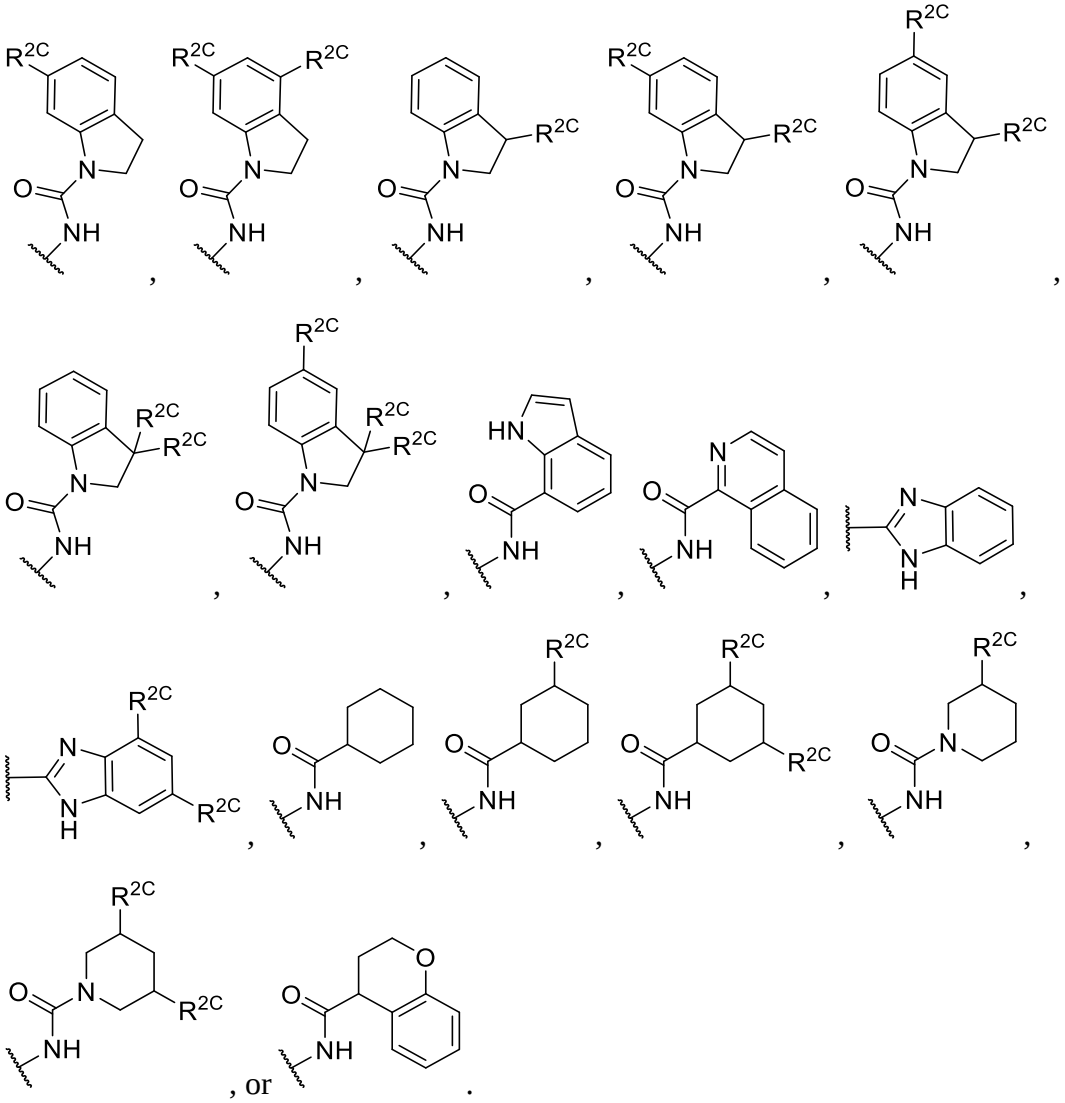
(c) R^{2A} is R^B substituted by r^2 instances of R^{2C};

(d) R^{2A} is phenyl; naphthyl; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms

independently selected from nitrogen, oxygen, and sulfur; wherein R^{2A} is substituted by r^2 instances of R^{2C}; or

(e) R^{2A} is , or .

11. The compound of any one of claims 1-9, wherein R^2 is , , ,



12. The compound of any one of the preceding claims, wherein each instance of:

(a) R^{2C} is independently halogen, -CN, -O-(C_{1-6} aliphatic), or C_{1-6} aliphatic; wherein each C_{1-6} aliphatic is optionally substituted with one or more halogen atoms; or

(b) R^{2C} is independently halogen or C_{1-3} aliphatic optionally substituted with 1-3 halogen.

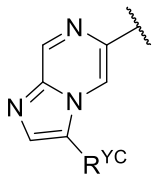
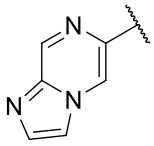
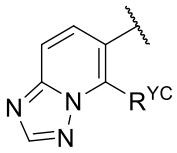
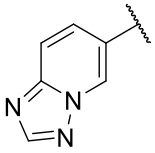
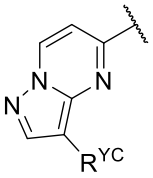
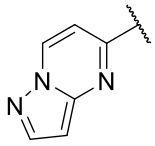
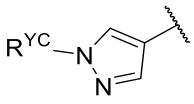
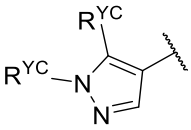
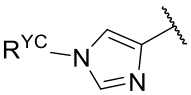
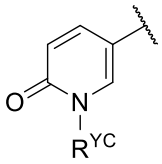
13. The compound of any one of the preceding claims, wherein Y is $C(R^{YA})$.

14. The compound of any one of the preceding claims, wherein R^{YA} is a C_{1-4} aliphatic chain; a 3-5 membered saturated or partially unsaturated monocyclic carbocyclic ring; or a 3-5 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein R^{YA} is substituted by r^6 instances of a group independently selected from halogen, -CN, -OH, -O-(optionally substituted C_{1-3} aliphatic), and an optionally substituted C_{1-3} aliphatic.

15. The compound of any one of claims 1-13, wherein:

(a) R^{YA} is an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said ring is substituted by r^6 instances of R^{YC};

(b) R^{YA} is a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted by r^6 instances of R^{YC}; or

(c) R^{YA} is , , , , , , , , , or .

16. The compound of any one of claims 1-13 or 15, wherein each instance of R^{YC} is independently oxo, halogen, -CN, -OH, -O-(C_{1-3} aliphatic), or C_{1-3} aliphatic, wherein each C_{1-3} aliphatic is optionally substituted with one or more halogen atoms.

17. A compound selected from those set forth in Table 1, or a pharmaceutically acceptable salt thereof.

18. A pharmaceutical composition, comprising a compound of any one of the preceding claims, and a pharmaceutically acceptable carrier.

19. Use of a compound of any of claims 1-17, or the pharmaceutical composition of claim 18, in the manufacture of a medicament for inhibiting PI3Kα signaling activity in a subject.

20. Use of a compound of any of claims 1-17, or the pharmaceutical composition of claim 18, in the manufacture of a medicament for treating a PI3Kα-mediated disorder in a subject.

21. Use of a compound of any of claims 1-17, or the pharmaceutical composition of claim 18, in the manufacture of a medicament for treating a cellular proliferative disease in a subject.

22. The use of claim 21, wherein the cellular proliferative disease is cancer.

23. The use of claim 22, wherein the cancer is breast cancer or ovarian cancer.

24. The use of claim 23, wherein the ovarian cancer is clear cell ovarian cancer.

25. The use of any one of claims 19-24, wherein the subject has PI3Kα containing at least one of the following mutations: H1047R, E542K, and E545K.

26. A compound of any of claims 1-17, or the pharmaceutical composition of claim 18, for use in therapy.